TERTIARY AMINO COMPOUNDS HAVING OPIOID RECEPTOR AFFINITY

This application claims the benefit of U.S. provisional no. 60/169,396 filed December 6, 1999, the disclosure of which is hereby incorporated by reference.

BACKGROUND OF THE INVENTION

Chronic pain is a major contributor to disability in the industrialized world and is the cause of an untold amount of suffering. The successful treatment of severe and chronic pain is a primary goal of the physician with opioid analgesics being the current drugs of choice. Unfortunately, this class of compounds produces several undesirable side effects including respiratory depression, constipation, and the development of tolerance and dependence.

Opioids are derived from the opium poppy *papaya somniferum* and include drugs such as morphine, codeine and semi-synthetic compounds derived from them and from thebaine, another component of the opium poppy. It was hypothesized that the opioids derived their therapeutic effect by interacting with specific receptor sites in the body. Later experiments led to the belief that there were more than one receptor site in the body, in explanation for the fact that the synthetic compound nalorphine provides analgesic activity while at the same time, antagonizes the analgesic effect of morphine.

Until recently, there was evidence of three major classes of opioid receptors in the central nervous system (CNS), with each class having subtype receptors. These receptor classes were designated as μ, δ and k. As opiates had a high affinity to these receptors while not being endogenous to the body, research followed in order to identify and isolate the endogenous ligands to these receptors. These ligands were identified as enkephalins, endorphins and dynorphins.

Recent experimentation has led to the identification of a cDNA encoding an opioid receptor-like (ORL1) receptor with a high degree of homology to the known receptor classes. This newly discovered receptor was classified as an opioid receptor based only on structural grounds, as the receptor did not exhibit pharmacological homology. It was initially demonstrated that non-selective ligands having a high affinity for μ, δ and k receptors had low affinity for the ORL1. This characteristic,

along with the fact that an endogenous ligand had not yet been discovered, led to the term "orphan receptor".

The science relating to opioid receptors presents an opportunity in drug discovery for novel compounds which can be administered for pain management or other syndromes modulated by these receptor. Such drug discovery could lead to compounds having a higher affinity for the μ, δ and k receptors than known compounds, while producing less side effects.

OBJECTS AND SUMMARY OF THE INVENTION

It is accordingly an object of the present invention to provide new compounds which exhibit affinity for opioid receptors.

It is another object of the present invention to provide new compounds which exhibit affinity for the opioid μ receptor.

It is another object of the present invention to provide new compounds for treating a patient suffering from chronic or acute pain by administering a compound having affinity for the opioid μ receptor.

It is another object of the invention to provide new compounds which have agonist activity at the μ receptor which is greater than compounds currently available e.g. morphine.

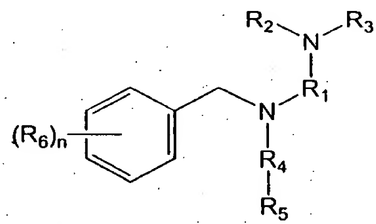
It is another object of the invention to provide methods of treating chronic and acute pain by administering compounds which have agonist activity at the μ receptor which is greater than compounds currently available.

It is another object of the invention to provide methods of treating chronic and acute pain by administering non-opioid compounds which have agonist activity at the μ receptor and which produce less side effects than compounds currently available.

It is another object of the invention to provide a method of reducing side effects associated with the administration of opioid analgesics in a human patient comprising administering to said human patient an analgesically effective amount of a non-opioid compound which exhibits a binding affinity specificity for the μ receptor as compared to the δ_2 receptor (K_i (nM) at the δ_2 receptor/ K_i (nM) at the μ receptor) of greater than about 250.

It is another object of the present invention to provide compounds useful as analgesics, antiinflammatories, diuretics, anesthetics and neuroprotective agents and methods for administering said compounds.

Other objects and advantages of the present invention will become apparent from the following detailed description thereof. With the above and other objects in view, the present invention comprises compounds having the general formula (I):



(I)

wherein

R_1 is selected from the group consisting of a bond and C_{1-10} alkyl, alkenyl or alkenylene;

R_2 and R_3 are independently selected from the group consisting of hydrogen and C_{1-10} alkyl, alkenyl or alkenylene

R_4 is selected from the group consisting of a bond and C_{1-10} alkyl, alkenyl or alkenylene, said C_{1-10} alkyl, alkenyl or alkenylene optionally substituted with 1-3 halogen or oxo groups;

R_5 is selected from the group consisting of hydrogen, a 5 or 6 membered aromatic or heteroaromatic group, and a C_{3-12} cycloalkyl;

R_6 is selected from the group consisting of C_{1-10} alkyl, C_{3-12} cycloalkyl and halogen; and

N is an integer from 0-3; and pharmaceutically acceptable salts thereof.

In preferred embodiments R_1 is selected from methyl or ethyl.

In other preferred embodiments R_2 is selected from methyl, ethyl, propyl and butyl.

In other preferred embodiments R_4 is selected from a bond, methyl or ethyl, wherein the methyl and ethyl are optionally substituted with an oxo group.

In other preferred embodiments R_5 is a 6-membered aryl ring, preferably phenyl.

As used herein, the term "alkyl" means a linear or branched saturated aliphatic hydrocarbon group having a single radical and 1-10 carbon atoms. Examples of alkyl groups include methyl, propyl, isopropyl, butyl, n-butyl, isobutyl, sec-butyl, tert-butyl, and pentyl. A branched alkyl means that one or more alkyl groups such as methyl, ethyl or propyl, replace one or both hydrogens in a $-CH_2-$ group of a linear alkyl chain.

The term "cycloalkyl" means a non-aromatic mono- or multicyclic hydrocarbon ring system having a single radical and 3-12 carbon atoms. Exemplary monocyclic cycloalkyl rings include cyclopropyl, cyclopentyl, and cyclohexyl. Exemplary multicyclic cycloalkyl rings include adamantyl and norbornyl.

The term "alkenyl" means a linear or branched aliphatic hydrocarbon group containing a carbon-carbon double bond having a single radical and 2-10 carbon atoms. A "branched" alkenyl means that one or more alkyl groups such as methyl, ethyl or propyl replace one or both hydrogens in a $-CH_2-$ or $-CH=$ linear alkenyl chain. Exemplary alkenyl groups include ethenyl, 1- and 2- propenyl, 1-, 2- and 3-butenyl, 3-methylbut-2-enyl, 2-propenyl, heptenyl, octenyl and decenyl.

The term "cycloalkenyl" means a non-aromatic monocyclic or multicyclic hydrocarbon ring system containing a carbon-carbon double bond having a single radical and 3 to 12 carbon atoms. Exemplary monocyclic cycloalkenyl rings include cyclopropenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl. An exemplary multicyclic cycloalkenyl ring is norbornenyl.

The term "aryl" means a carbocyclic aromatic ring system containing one, two or three rings which may be attached together in a pendent manner or fused, and containing a single radical. Exemplary aryl groups include phenyl and naphthyl.

The term "heteroaryl" means unsaturated heterocyclic radicals, wherein heterocyclic is as previously described. Exemplary heteroaryl groups include unsaturated 3 to 6 membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, such as pyrrolyl, pyridyl, pyrimidyl, and pyrazinyl; unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, such as indolyl, quinolyl, isoquinolyl; unsaturated 3 to 6- membered heteromonocyclic groups containing an oxygen atom, such as furyl; unsaturated 3 to 6 membered heteromonocyclic groups

containing a sulfur atom, such as thienyl; unsaturated 3 to 6 membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as oxazolyl; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as benzoxazolyl; unsaturated 3 to 6 membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, such as thiazolyl; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, such as benzothiazolyl. The term “heteroaryl” also includes unsaturated heterocyclic radicals, wherein heterocyclic is as previously described, in which the heterocyclic group is fused with an aryl group, in which aryl is as previously described. Exemplary fused radicals include benzofuran, benzdioxole and benzothiophene.

As used herein, the term “patient” includes both human and other mammals.

As used herein, the term “halogen” includes fluoride, bromide, chloride, iodide or alabamide.

As used herein, the term “specificity” with respect to opioid receptors is obtained by dividing the K_i (nM) at one opioid receptor by the K_i (nM) at another receptor (higher K_i/lower K_i.

The invention disclosed herein is meant to encompass all pharmaceutically acceptable salts thereof of the disclosed compounds. The pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salt, potassium salt, secium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like; inorganic acid salts such as hydrochloride, hydrobromide, sulfate, phosphate and the like; organic acid salts such as formate, acetate, trifluoroacetate, maleate, tartrate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate, and the like; amino acid salts such as arginate, asparginate, glutamate and the like.

The invention disclosed herein is also meant to encompass all prodrugs of the disclosed compounds. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug in vivo.

The invention disclosed herein is also meant to encompass the in vivo metabolic products of the disclosed compounds. Such products may result for

example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled compound of the invention, administering it parenterally in a detectable dose to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur and isolating its conversion products from the urine, blood or other biological samples.

The invention disclosed herein is also meant to encompass the disclosed compounds being isotopically-labelled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Some of the compounds disclosed herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present invention is also meant to encompass all such possible forms as well as their racemic and resolved forms and mixtures thereof. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended to include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present invention as well.

As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

The term "chiral center" refers to a carbon atom to which four different groups are attached.

The term "enantiomer" or "enantiomeric" refers to a molecule that is nonsuperimposeable on its mirror image and hence optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image rotates the plane of polarized light in the opposite direction.

The term "racemic" refers to a mixture of equal parts of enantiomers and which is optically inactive.

The term "resolution" refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule.

Sub A1

Certain preferred compounds according to the invention include:

1-benzylamino-3-dibutylamino-propyl;

1-[1-benzyl-1-(2-phenyl-1-oxo-ethyl)-amino]-2-diethylamino-ethyl;

1-[1-benzyl-1-(2-phenyl-1-oxo-ethyl)-amino]-2-dibutylamino-ethyl; and pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention can be administered to anyone requiring modulation of the μ receptors. Administration may be orally, topically, by suppository, inhalation, or parenterally.

The present invention also encompasses all pharmaceutically acceptable salts of the foregoing compounds. One skilled in the art will recognize that acid addition salts of the presently claimed compounds may be prepared by reaction of the compounds with the appropriate acid via a variety of known methods.

Various oral dosage forms can be used, including such solid forms as tablets, gelcaps, capsules, caplets, granules, lozenges and bulk powders and liquid forms such as emulsions, solution and suspensions. The compounds of the present invention can be administered alone or can be combined with various pharmaceutically acceptable carriers and excipients known to those skilled in the art, including but not limited to diluents, suspending agents, solubilizers, binders, disintegrants, preservatives, coloring agents, lubricants and the like.

When the compounds of the present invention are incorporated into oral tablets, such tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, multiply compressed or multiply layered. Liquid oral dosage forms include aqueous and nonaqueous solutions, emulsions, suspensions, and solutions and/or suspensions reconstituted from non-effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, coloring agents, and flavoring agents. When the compounds of the present invention are to be injected parenterally, they may be, e.g., in the form of an isotonic sterile

solution. Alternatively, when the compounds of the present invention are to be inhaled, they may be formulated into a dry aerosol or may be formulated into an aqueous or partially aqueous solution.

In addition, when the compounds of the present invention are incorporated into oral dosage forms, it is contemplated that such dosage forms may provide an immediate release of the compound in the gastrointestinal tract, or alternatively may provide a controlled and/or sustained release through the gastrointestinal tract. A wide variety of controlled and/or sustained release formulations are well known to those skilled in the art, and are contemplated for use in connection with the formulations of the present invention. The controlled and/or sustained release may be provided by, e.g., a coating on the oral dosage form or by incorporating the compound(s) of the invention into a controlled and/or sustained release matrix.

Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms, are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986), incorporated by reference herein. Techniques and compositions for making solid oral dosage forms are described in Pharmaceutical Dosage Forms: Tablets (Lieberman, Lachman and Schwartz, editors) 2nd edition, published by Marcel Dekker, Inc., incorporated by reference herein. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also described in Remington's Pharmaceutical Sciences (Arthur Osol, editor), 1553B1593 (1980), incorporated herein by reference. Techniques and composition for making liquid oral dosage forms are described in Pharmaceutical Dosage Forms: Disperse Systems, (Lieberman, Rieger and Banker, editors) published by Marcel Dekker, Inc., incorporated herein by reference.

When the compounds of the present invention are incorporated for parenteral administration by injection (e.g., continuous infusion or bolus injection), the formulation for parenteral administration may be in the form of suspensions, solutions, emulsions in oily or aqueous vehicles, and such formulations may further comprise pharmaceutically necessary additives such as stabilizing agents, suspending agents, dispersing agents, and the like. The compounds of the invention may also be in the form of a powder for reconstitution as an injectable formulation.

The dose of the compounds of the present invention is dependent upon the affliction to be treated, the severity of the symptoms, the route of administration, the frequency of the dosage interval, the presence of any deleterious side-effects, and the particular compound utilized, among other things.

The following examples illustrate various aspects of the present invention, and are not to be construed to limit the claims in any manner whatsoever.

put A2

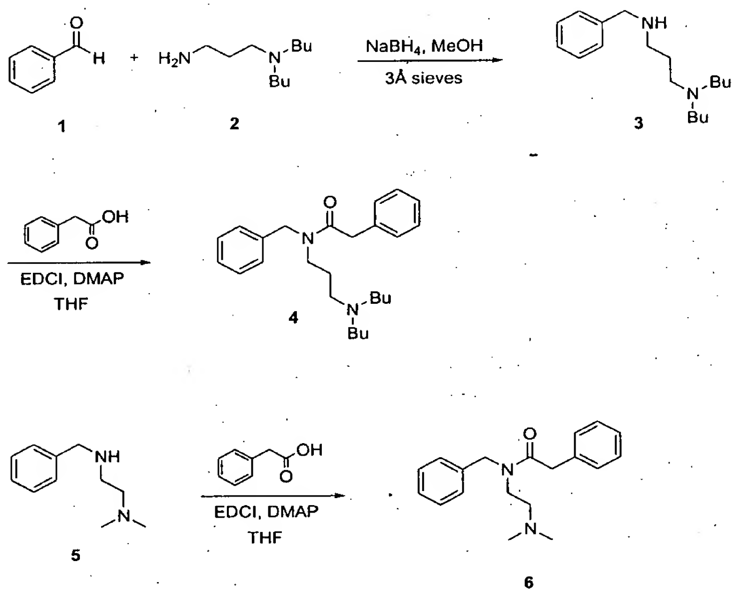
Examples 1-3

1-benzylamino-3-dibutylamino-propyl (Example 1);

1-[1-benzyl-1-(2-phenyl-1-oxo-ethyl)-amino]-2-dibutylamino-ethyl (Example 2); and

1-[1-benzyl-1-(2-phenyl-1-oxo-ethyl)-amino]-2-diethylamino-ethyl (Example 3).

The above compounds were synthesized according to the following synthetic scheme and general procedure:



Compound 3 (Example 1)

To a solution of benzaldehyde (**1**, 3.1 g, 29.5 mmol) in anhydrous methanol was added 3-(dibutylamino)propylamine (**2**, 5 g, 26.8 mmol). After stirring 1 h in the presence of 3Å molecular sieves, sodium borohydride (1.0 g, 26.8 mmol) was added. After stirring another 16 hours, the reaction was filtered, and the sieves were washed with dichloromethane. Water was added, and the phases were separated. The aqueous phase was made basic by addition of 15% aqueous NaOH, and it was then extracted with dichloromethane. The combined organic extracts were washed with water, washed with brine, dried with sodium sulfate, and concentrated. Silica gel chromatography eluting with 20:2:1 hexane–ethyl acetate–triethylamine provided compound **3** as a colorless oil: ^{1}H NMR data (300 MHz, $CDCl_3$): δ 0.88 (t, 6H, J = 7.0 Hz), 1.26 (m, 4H), 1.37 (m, 4H), 1.64 (m, 2H), 2.35 (t, 4H, J = 8.0 Hz), 2.43 (t, 2H, J = 7.0 Hz), 2.64 (t, 2H, J = 6.8 Hz), 3.75 (s, 2H), 7.15–7.40 (m, 5H).

Compound 4 (Example 2)

To a solution of compound **3** (500 mg, 1.81 mmol) in anhydrous THF was added phenylacetic acid (246 mg, 1.81 mmol), EDCI (520 mg, 2.71 mmol), and DMAP (442 mg, 3.62 mmol), and the reaction mixture was allowed to stir 15 h. Water and dichloromethane were added, and the layers were separated. The aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with 5% HCl, washed with saturated aqueous sodium bicarbonate, washed with water, washed with brine, dried with sodium sulfate, and concentrated. Silica gel chromatography eluting with 20:2:1 hexane–ethyl acetate–triethylamine provided compound **4** as a colorless oil: ^{1}H NMR data (300 MHz, $CDCl_3$): (2 rotamers) δ 2.20 (m, 6H), 1.25–1.90 (m, 8H), 1.58 (m, 1.2H), 1.68 (m, 0.8H), 2.15 (m, 6H), 3.25 (t, 1.2H, J = 7.4 Hz), 3.40 (t, 0.8H, J = 6.9 Hz), 3.68 (s, 0.8H), 3.80 (s, 1.2H), 4.50 (s, 0.8H), 4.63 (s, 1.2H), 7.05–7.45 (m, 10H).

Compound 6 (Example 3)

To a solution of *N'*-benzyl-*N,N*-dimethylethylenediamine (**5**, 500 mg, 2.8 mmol) in anhydrous THF was added phenylacetic acid (382 mg, 2.8 mmol), EDCI (805 mg, 4.2 mmol), and DMAP (684 mg, 5.6 mmol), and the reaction mixture was allowed to stir 15 h. Water and dichloromethane were added, and the layers were

separated. The aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with 5% HCl, washed with saturated aqueous sodium bicarbonate, washed with water, washed with brine, dried with sodium sulfate, and concentrated. Silica gel chromatography eluting with 10:2:1 hexane–ethyl acetate–triethylamine provided compound **6** as a colorless oil: ^{1}H NMR data (300 MHz, $CDCl_3$): (2 rotamers) δ 2.15 (s, 2.4H), 2.20 (s, 3.6H), 2.29 (t, 0.8H, J = 6.9 Hz), 2.44 (t, 1.2H, J = 7.4 Hz), 3.30 (t, 0.8H, J = 6.9 Hz), 3.48 (t, 1.2H, J = 7.4 Hz), 3.70 (s, 1.2H), 3.81 (s, 0.8H), 4.57 (s, 1.2H), 4.64 (s, 0.8H), 7.10–7.35 (m, 10H).

The general procedures disclosed above can be modified in order to synthesize the other preferred compounds of the invention.

Example 4

Affinity at the μ, k and δ receptors for preferred compounds was obtained according to the following assays:

Mu, kappa or delta opioid receptor membrane solution was prepared by sequentially adding final concentrations of 0.075 μg/μl of the desired membrane protein, 10 μg/ml saponin, 3 μM GDP and 0.20 nM [^{35}S]GTPγS to binding buffer (100 mM NaCl, 10 mM $MgCl_2$, 20 mM HEPES, pH 7.4) on ice. The prepared membrane solution (190 μl/well) was transferred to 96-shallow well polypropylene plates containing 10 μl of 20x concentrated stock solutions of agonist prepared in DMSO. Plates were incubated for 30 min at room temperature with shaking. Reactions were terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Packard) using a 96-well tissue harvester (Brandel) and followed by three filtration washes with 200 μl ice-cold binding buffer (10 mM NaH_2PO_4, 10 mM Na_2HPO_4, pH 7.4). Filter plates were subsequently dried at 50°C for 2-3 hours. Fifty μl/well scintillation cocktail (MicroScint20, Packard) was added and plates were counted in a Packard Top-Count for 1 min/well.

Data were analyzed using the curve fitting functions in GraphPad PRISM™, v. 3.0 and the results are set forth in table 1 below:

TABLE 1

	calc K_i (nM)		
Compound	**μ**	**k**	δ_2
1-[1-benzyl-1-(2-phenyl-1-oxo-ethyl)-amino]-2-dibutylamino-ethyl	40	3500	>10,000